UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,490	10/14/2005	Pavel V. Bondarenko	12671-007US1	4633

26181 7590 11/21/2008

FISH & RICHARDSON P.C.
PO BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
XU, XIAOYUN	

ART UNIT	PAPER NUMBER
1797	

NOTIFICATION DATE	DELIVERY MODE
11/21/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/511,490	BONDARENKO ET AL.	
	Examiner	Art Unit	
	ROBERT XU	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-74* is/are pending in the application.

4a) Of the above claim(s) *1-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/15/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Preliminary Amendment filed on 10/15/2004 is acknowledged. Claims 1-43 are cancelled. Claims 44-74 are pending in the application and are considered on merits

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. **Claims 44-63** are rejected under 35 U.S.C. 103(a) as being unpatentable over Gygi et al. (Nature Biotechnology, 1999, IDS) (Gygi).

In regard to Claim 44, Gygi teaches a method for quantifying peptides in a peptide mixture. The method comprises

receiving a first peptide mixture containing a plurality of peptides (tagged with light form of reagent) (see page 994, right col. 3rd paragraph);

separating the plurality of peptide of the first mixture over a period of time (see page 994, right col. 3rd paragraph);

mass-to-charge analyzing the separated peptides of the first peptide mixture at a particular time in the period of time (see page 994, right col. 3rd paragraph, page 995 and Figure 2);

calculating an abundance of the mass analyzed peptides of the first peptide mixture (see page 994, right col. 3rd paragraph, page 995 and Figure 2);

calculating a relative quantity for mass analyzed peptides of the first peptide mixture by comparing the calculated abundance of mass analyzed peptides of the first peptide mixture (tagged with light form of reagent) with an abundance of peptides in a reference sample (tagged with heavy form of reagent) (see page 994, right col. 3rd paragraph).

Gygi does not teach that the reference sample is external to the first peptide mixture. Applicant is advised that the rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. (see KSR, 550 U.S. at ___, 82 USPQ2d at 1395) (see MPEP 2143). In that regard, using internal or external reference in mass spectrometry is well known in the art. When the mass-to-charge signal of reference does not overlap with the signal of the target sample, the reference can be used as an internal and/or an external reference. When the mass-to-charge signal of the reference overlaps with the signal of the target sample, then the reference can only be used as an external reference. Therefore, the choice of internal and external reference is an obvious variation in mass spectrometry analysis. In Gygi's case, the signal of the reference does not overlap with the target sample; therefore, either internal or external reference can be used. Gygi choose to use internal reference so that the reference is measured under the exactly the same condition as the target sample. At time of the invention, it would have been obvious for a person of ordinary skill in the art to decide whether an internal reference or an external reference is more suitable for the mass spectrometry analysis.

In regard to Claim 45, Gygi teaches digesting a first polypeptide sample to generate the first peptide mixture (see page 994, right col. 3rd paragraph).

In regard to Claim 46, Gygi teaches preparing the reference sample by digesting a second polypeptide sample (see page 994, right col. 3rd paragraph);

separating peptides from the digested second polypeptide sample (see page 994, right col. 3rd paragraph);

mass analyzing the separated peptide from the digested second polypeptide sample (see page 994, right col. 3rd paragraph, page 995, left col. 1st paragraph); and

calculating an abundance of mass analyzed peptides from the second polypeptide sample (see page 994, right col. 3rd paragraph);

calculating relative quantity for the mass analyzed peptides of the first peptide mixture by comparing the calculated abundance of mass analyzed peptides of the first peptide mixture (tagged with light form of reagent) with the calculated abundance of corresponding mass analyzed peptide from the second polypeptide sample (tagged with heavy form of reagent) (see page 994, right col. 3rd paragraph).

In regard to Claims 47 and 48, Gygi teaches separating peptides by liquid chromatography, isolating a liquid chromatography eluent at the particular time and mass analysis the isolated eluent (LC-MS/MS) (see page 994, right col. 3rd paragraph).

In regard to Claims 49-51, Gygi teaches fragmenting an ion derived from a peptide of separated peptides and mass analyzing fragments of the ion (LC-MS/MS) and identifying peptides in the first sample by searching a sequence database based on mass analysis information for the fragments (see page 995).

In regard to Claim 52, Gygi teaches reconstructing a chromatogram peak for a peptide based on mass analysis information for the peptide (see page 996 and Figure 3).

In regard to Claim 53, Gygi teaches calculating an abundance of a peptide based on a reconstructed chromatogram peak area for the peptide (see page 996 right col.)

In regard to Claim 54, Gygi does not specifically teach using only chromatogram peaks located within a threshold distance in the reconstructed chromatogram of the particular time. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In that regard, it is well know in chromatography that each eluent peak has a retention time that corresponds to its peak intensity. Therefore, it would have been obvious to a person of

ordinary skill in the art to run MS analysis at the retention time that is as close to the peak retention time as possible in order to obtain the highest intensity of MS chromatogram. The optimum threshold distance from the peak retention time can be obtained by routine experimentation.

In regard to Claim 55, Gygi teaches calculating a relative quantity of mass analyzed peptides by comparing an abundance calculated by reconstructing a chromatogram peak area for a peptide of the first peptide mixture (tagged with light form of reagent) with an abundance calculated by reconstructing a chromatogram peak area for a peptide in the reference sample (tagged with heavy form of reagent) (see page 996, left co. 3rd paragraph, right col. and Figure 3).

In regard to Claims 56 and 57, Gygi teaches normalizing the calculated abundance of mass analyzed peptides of the first peptide mixture (tagged with the light form of the reagent) based on an internal standard (tagged with the heavy form of the reagent) that is added to the first polypeptide sample (see page 996, Table 1).

In regard to Claim 58, Gygi does not teach normalizing the calculated abundance based on an external standard. As has been discussed with respect to claim 1 above, external standard is an obvious variation of internal standard. At time of the invention, it would have been obvious for a person of ordinary skill in the art to decide whether an internal reference or an external reference is more suitable for normalization analysis.

In regard to Claim 59, Gygi teaches identifying a plurality of peptides of the first peptide mixture based on the MS/MS analysis and combining the results generated from MS and MS/MS analysis to calculate (determine) a relative quantity for each of the identified peptides (see page 995).

In regard to Claim 60, Gygi teaches that the relative quantification is determined by the ratio of reconstructed chromatogram peak area of the peptide pairs (see page 995). In other words, the relative quantification is determined by calculating the correction factor based on reconstructed chromatogram peak area of the peptide. Gygi does not specifically teach calculating a single correction factor for a set of peptides in the first peptide mixture. However, when correction factors are calculated for each of the peptides in the first peptide mixture, a single correction factor for the peptide set in the

first peptide mixture can be calculated in a similar way based on a single reference. It would have been obvious to a person of ordinary skill in the art to calculate a single correction factor for the peptide set in the first peptide mixture based on a single reference in a same way as taught by Gygi.

In regard to Claim 61, Gygi teaches mass-to-charge analyzing and calculating an abundance for arbitrary peptides of the first peptide mixture (see page 995).

In regard to Claim 62, Gygi teaches a method of quantifying peptides in a mixture. The method comprises

digesting a protein sample to generate a mixture of peptides (see page 994, right col. 3rd paragraph);

separating peptide mixture by liquid chromatography (see page 994, right col. 3rd paragraph);

mass analyzing the separated peptides (see page 994, right col. 3rd paragraph, page 995 and Figure 2);

identifying the mass analyzed peptide based on mass spectra for the peptides (see page 994, right col. 3rd paragraph, page 995 and Figure 2);

calculating chromatogram peak area for identified peptides (see page 996, Figure 3C);

calculating chromatogram peak area for proteins corresponding to the identified peptides (see page 996, Figure 3C);

normalizing the chromatogram peak area for the protein based on a chromatogram peak area for an internal standard (tagged with isotopically heavy form of reagent) (see page 996, Table 1).

determining a relative quantity for a protein by comparing the normalized chromatogram peak area for the protein to a chromatogram peak area for a corresponding protein in a reference sample (see page 996, Table 1).

In regard to Claim 63, Gygi teaches an apparatus for quantifying peptides in a peptide mixture. The apparatus comprises

means for receiving a first peptide mixture containing a plurality of peptides (tagged with isotopically light form of reagent) (see page 994, right col. 3rd paragraph);

means for separating the plurality of peptides of the first peptide mixture over a period of time (see page 994, right col. 3rd paragraph);

means for mass analyzing the separated peptides of the first peptide mixture at a particular time in the period of time (see page 994, right col. 3rd paragraph, page 995);

means for calculating an abundance of the mass analyzed peptides of the first peptide mixture (see page 994, right col. 3rd paragraph, page 995);

means for calculating a relative quantity for mass analyzed peptides of the first peptide mixture by comparing the calculated abundance of the mass analyzed peptides of the first peptide mixture (tagged with isotopically light form of reagent) with an abundance of peptides in a reference sample (tagged with isotopically heavy form of reagent) (see page 994, right col. 3rd paragraph, page 995);

Gygi does not teach that the reference sample is external to the first peptide mixture. Using internal or external reference in mass spectrometry is well known in the art. The choice of internal and external reference is an obvious variation in mass spectrometry analysis. At time of the invention, it would have been obvious for a person of ordinary skill in the art to decide whether an internal reference or an external reference is more suitable for the mass spectrometry analysis.

In regard to Claims 64 and 65, Gygi teaches apparatus that also receives one additional peptide mixture (tagged with isotopically heavy form of reagent) as reference sample (see page 994, right col. 3rd paragraph).

In regard to Claim 66, Gygi teaches that peptides are quantified by measuring the relative signal intensities for pairs of peptide ions of identical sequence in the first peptide mixture (tagged with the isotopically light form of the reagent) and the reference sample (tagged with isotopically heavy form of the reagent) (see page 994, right col. 3rd paragraph).

In regard to Claim 67, Gygi teaches mass-to-charge analyzing and calculating an abundance for arbitrary peptides of the first peptide mixture (see page 995, Figure 2 and 3).

In regard to Claim 68, Gygi teaches separating, mass-to-charge analyzing and calculating an abundance for peptides of the subject peptides (see page 994, right col.

3rd paragraph, page 995). Gygi's method requires at least one cysteinyl residue present in the peptide in order to be tagged with the isotope reagent. Therefore, Gygi does not teach handling peptides independent of a particular amino acids composition. However, using internal or external reference in mass spectrometry is well known in the art. When external reference is used, isotope tag reagent will not be needed and therefore, the presence of cysteinyl residue in the peptide will not be required. At time of the invention it would have been obvious for a person of ordinary skill in the art to use external reference sample in Gygi's apparatus to handle peptide that does not have cysteinyl residue.

In regard to Claims 69 and 70, Gygi discloses computer program for automatically separating peptides of peptide mixture; mass-to-charge analyzing the separated peptides; and calculating relative quantity and abundance of the mass analyzed peptides by comparing the abundance of the peptides in the first peptide mixture with the abundance of the corresponding peptides in the reference sample and comparing normalized chromatogram peak area for the protein with a chromatogram peak area for a corresponding protein in a reference sample. (see page 994, right col. 3rd paragraph, page 995).

The Courts have held that to provide a mechanical or automatic means to replace manual activity, which accomplishes the same result, is within the ambit of a person of ordinary skill in the art. See In re Venner, 120 USPQ 192 (CCPA 1958) (see MPEP section 2144.04). Therefore, it would have been obvious to one of ordinary skill in the art to automate the procedure.

In regard to Claim 71, Gygi discloses an apparatus for quantifying peptides in a first peptide mixture. The apparatus comprises digital circuitry configured to perform the following actions:

receiving separation information representing a separation of a plurality of peptides of a first peptide mixture over a period of time (see page 994, right col. 3rd paragraph);

receiving mass-to-charge analysis information for the separated peptides of the first peptide mixture at a particular time in the period of time (see page 994, right col. 3rd paragraph, page 995);

calculating an abundance of the mass analyzed peptides of the first peptide mixture (see page 994, right col. 3rd paragraph, page 995); and

calculating a relative quantity for the mass analyzed peptides of the first peptide mixture by comparing the calculated abundance of the mass analyzed peptides of the first peptide mixture with an abundance of the peptides in a reference sample, the reference sample being external to the first peptide mixture (see page 994, right col. 3rd paragraph, page 995);

Gygi does not teach that the reference sample is external to the first peptide mixture. Using internal or external reference in mass spectrometry is well known in the art. The choice of internal and external reference is an obvious variation in mass spectrometry analysis. At time of the invention, it would have been obvious for a person of ordinary skill in the art to decide whether an internal reference or an external reference is more suitable for the mass spectrometry analysis.

In regard to Claim 72, Gygi discloses an apparatus for quantifying peptides in a first peptide mixture. The apparatus comprises digital circuitry configured to perform the following actions:

receiving separation information representing a separation of a plurality of peptides of a first peptide mixture over a period of time (see page 994, right col. 3rd paragraph);

receiving mass-to-charge analysis information for the separated peptides of the first peptide mixture at a particular time in the period of time (see page 994, right col. 3rd paragraph);

identifying the mass analyzed peptides based on the mass-to-charge analysis information for the peptides (see page 994, right col. 3rd paragraph, page 995);

calculating chromatogram peak areas for the identified peptides (see page 994, right col. 3rd paragraph, page 995);

calculating chromatogram peak areas for proteins corresponding to the identified peptides based on the calculated peak areas for the corresponding peptides (see page 994, right col. 3rd paragraph, page 995);

normalizing the chromatogram peak area for the protein based on a chromatogram peak area for an internal standard (see page 994, right col. 3rd paragraph, page 995); and

determining a relative quantity for a protein of the of the proteins by comparing the normalized chromatogram peak area for the protein to a chromatogram peak area for a corresponding protein in a reference sample (see page 994, right col. 3rd paragraph, page 995).

In regard to Claims 73 and 74, Gygi teaches a method and apparatus for quantifying peptides in a biological sample. Gygi does not specifically teach that the method and apparatus can also be used for quantifying compounds in a biological sample. The court has held that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim (see MPEP 7.37.09). In that regards, the processes and apparatus recited in the instant claims can be derived from Gygi's teaching by simply substituting peptide with the compound (see page 994, right col. 3rd paragraph, page 995). At the time of the invention it would have been obvious for a person of ordinary skill in the art to use Gygi's method and apparatus for quantifying compound in a biological sample.

Conclusion

4. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

LaDine et al. (US 2002/0068366) (LaDine) teaches a method of mass spectrometry analysis for quantifying proteins in a biological system after exposing the biological system to a stimulus.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT XU whose telephone number is (571)270-

5560. The examiner can normally be reached on Mon-Thur 7:30am-5:00pm, Fri 7:30am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on (571)272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

11/18/2008

/Yelena G. Gakh/
Primary Examiner, Art Unit 1797

RX